DOI:
10.1093/schbul/sbw151

Document Version
Publisher's PDF, also known as Version of record

Schizophrenia Bulletin vol. 43 no. 1 pp. 48–56, 2017
doi:10.1093/schbul/sbw151

Diagnostic and Prognostic Significance of Brief Limited Intermittent Psychotic Symptoms (BLIPS) in Individuals at Ultra High Risk

Paolo Fusar-Poli*[,1,2], Marco Cappucciati[1,3], Andrea De Micheli[1,3], Grazia Rutigliano[1,4], Ilaria Bonoldi[1,2], Stefania Tognin[1,2], Valentina Ramella-Cravaro[1,5], Augusto Castagnini[6], and Philip McGuire[1]

[1]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [2]OASIS Service, South London and the Maudsley NHS Foundation Trust, London, UK; [3]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy; [4]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [5]Department of Neurofarba, University of Florence, Florence, Italy; [6]Postgraduate School of Child Neuropsychiatry, University of Modena and Reggio Emilia, Modena, Italy

*To whom correspondence should be addressed; Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, 5th Floor, PO63, 16 De Crespigny Park, SE5 8AF London, UK; tel: +44-(0)-20-7848-0900, fax: +44-(0)-207-848-0976, e-mail: paolo.fusar-poli@kcl.ac.uk

Background: **Brief Limited Intermittent Psychotic Symptoms (BLIPS) are key inclusion criteria to define individuals at ultra high risk for psychosis (UHR). Their diagnostic and prognostic significance is unclear.** ***Objectives:*** **To address the baseline diagnostic relationship between BLIPS and the ICD-10 categories and examine the longitudinal prognostic impact of clinical and sociodemographic factors.** ***Methods:*** **Prospective long-term study in UHR individuals meeting BLIPS criteria. Sociodemographic and clinical data, including ICD-10 diagnoses, were automatically drawn from electronic health records and analyzed using Kaplan–Meier failure function (1-survival), Cox regression models, bootstrapping methods, and Receiver Operating Characteristics (ROC) curve.** ***Results:*** **Eighty BLIPS were included. At baseline, two-thirds (68%) of BLIPS met the diagnostic criteria for ICD-10 Acute and Transient Psychotic Disorder (ATPD), most featuring schizophrenic symptoms. The remaining individuals met ICD-10 diagnostic criteria for unspecified nonorganic psychosis (15%), mental and behavioral disorders due to use of cannabinoids (11%), and mania with psychotic symptoms (6%). The overall 5-year risk of psychosis was 0.54. Recurrent episodes of BLIPS were relatively rare (11%) but associated with a higher risk of psychosis (hazard ratio [HR] 3.98) than mono-episodic BLIPS at the univariate analysis. Multivariate analysis revealed that seriously disorganizing or dangerous features increased greatly (HR = 4.39) the risk of psychosis (0.89 at 5-year). Bootstrapping confirmed the robustness of this predictor (area under the ROC = 0.74).** ***Conclusions:*** **BLIPS are most likely to fulfill the ATPD criteria, mainly acute schizophrenic subtypes. About half of BLIPS cases develops a psychotic disorder during follow-up. Recurrent BLIPS are relatively rare but tend to develop into psychosis. BLIPS with seriously disorganizing or dangerous features have an extreme high risk of psychosis.**

Key words: psychosis/schizophrenia/risk/UHR/BLIPS/brief psychosis/prevention/diagnosis/CAARMS

Introduction

Brief Limited Intermittent Psychotic Symptoms (BLIPS), are 1 of the 3 operational definitions for individuals at ultra high risk for psychosis (UHR[1]), that were incorporated into the Comprehensive Assessment of At Risk Mental State (CAARMS),[2] along with Attenuated Psychosis Symptoms (APS) and Genetic Risk and Deterioration Syndrome (GRD). BLIPS identify a group of "young people with a history of fleeting psychotic experiences that spontaneously resolved within one week" (page 8 in Yung et al[3]), without the use of antipsychotic. Under the UHR paradigm, BLIPS are not considered psychotic and do not receive a diagnosis of full-blown psychosis. This makes the psychosis threshold of the UHR paradigm different from that of current psychiatric classifications such as ICD and DSM.[4]

The actual diagnostic significance of the BLIPS subgroup is unknown. Although it has been recommended that BLIPS should be contrasted against operationally based ICD/DSM psychotic disorders (page 706 Miller et al[5]), no comparative studies have yet been conducted, and hence their relationship deserve clarification. The

prognostic significance of BLIPS is also unclear. A first recent meta-analysis from our group has compared the risk of psychosis onset across different UHR subgroups, indicating that the BLIPS have a distinct profile, with higher risk of psychosis than the APS and GRD subgroups.[6] Another meta-analysis from our group compared the BLIPS against standard ICD-10 and DSM-5 categories of brief psychotic episodes. BLIPS were found to have the same risk of psychotic recurrence as the ICD-10 category of Acute and Transient Psychotic Disorder (ATPD) and DSM-5 "Brief psychotic disorder,"[7] while they have a lower risk than remitted cases of first-episode schizophrenia.[7] However, this meta-analysis did not test whether the diagnoses overlapped at baseline or if the same patient could actually be diagnosed with both competing constructs. Furthermore, the exact longitudinal course of the BLIPS is still not completely clear. Little is known about clinical and sociodemographic factors predicting BLIPS outcome. This is probably because case identification is difficult owing to the fleeting features and the small number of BLIPS, accounting only for about 10% of UHR samples.[6] For example, although BLIPS cases are by definition "intermittent," the actual proportion and the longitudinal course of recurrent vs mono-episodic BLIPS is unknown. More to the point, the Structured Interview for Prodromal Symptoms (SIPS) and its companion Scale of Prodromal Symptoms (SOPS),[8] that also address UHR symptoms, have introduced a close variant of the BLIPS, ie, "Brief Intermittent Psychotic Symptoms" (BIPS). The SIPS considers "seriously disorganizing or dangerous" features as fully psychotic and not as at risk BIPS symptoms. Conversely, these features are not routinely assessed with the CAARMS and therefore do not constitute exclusion criteria for BLIPS cases (for details on the differences between BLIPS and BIPS see table 1 in Fusar-Poli et al[9]). Yet, the rationale for considering seriously disorganizing or dangerous features fully psychotic and beyond the UHR state (under the BIPS construct) rather than as UHR symptoms (under the BLIPS construct) was not clarified by the SIPS/SOPS authors. Since these differences constitute an important source of disagreement between the CAARMS and the SIPS[10] it is important to explore the actual prognostic significance of seriously disorganizing or dangerous features within the BLIPS framework.

We present here the first long-term prospective study in the largest sample of BLIPS individuals to date, assessed and treated by a clinical service for UHR individuals.[11] The first aim of this study is to address the diagnostic significance of the BLIPS, by investigating their relationship with competing ICD-10 diagnoses. The second aim of this study is to address the prognostic significance of BLIPS by exploring the impact of sociodemographic and clinical predictors of psychosis onset.

Methods

Sample

We included all individuals referred for suspicion of psychosis risk to the Outreach and Support in South London (OASIS) UHR service, NHS Foundation Trust,[11] who met the BLIPS CAARMS 12/2006 criteria[2] up to December 2015. The OASIS team is specialized in detecting and treating individuals at UHR for psychosis. It currently covers a catchment area of about 1.3 million of individuals in South London (Lambeth, Southwark, Lewisham, Croydon), where there is one of the highest rates of psychosis in the world and therefore a large proportion of BLIPS among UHR individuals.[6]

Design

Prospective long-term study in UHR individuals who met BLIPS criteria.

Clinical Assessment

UHR Assessment. The details of the psychopathological UHR assessment conducted at the OASIS have been described previously.[11] In brief, the UHR assessment is based on the CAARMS 12/2006.[2] At the end of the assessment the individuals are diagnosed as UHR (APS and/or BLIPS and/or GRD), not at risk or already psychotic. Clinical follow-up is usually performed as part of the standard care. Furthermore, the clinical team offers focused interventions spanning pharmacological, psychological and psychoeducational activities for 2 years.[12]

ICD-10 Diagnoses. The BLIPS is not a codable diagnosis. Therefore, the local NHS Trust requires BLIPS individuals to be additionally assigned a psychiatric diagnosis according to ICD-10. The diagnostic decision is formulated by psychiatrists working at the OASIS, under the supervision of the 2 consultants who have a long-standing expertise in the assessment of UHR cases.

Seriously Disorganizing or Dangerous. The notion of seriously disorganizing or dangerous symptom is introduced in the SIPS manual with the concept of "urgency" (pages 14–15 in McGlashan et al[13]). This is defined as follows: "urgency is any positive psychotic symptom that is seriously disorganizing or dangerous no matter what the duration".[13] Further details are provided on page 31 of the SIPS manual with the comparative SIPS vs CAARMS table,[13] and on page 50 of the SIPS manual, where the following example can be found: "an example of a 6 rating on perceptual abnormalities is a patient reporting that he hears the devil speaking to him and telling him to hurt himself. He believes the voice is real and he believes that he should act on the command. This symptom meets criteria for being dangerous as well, and the patient

would immediately meet criteria for current psychosis."[13] Professor Scott Woods provided additional material and a revised version of the features, which runs as follows: "'dangerous' is taken to mean physically dangerous e.g. risk of death or serious physical injury, and 'disorganizing' means potentially psychosocially dangerous, e.g. risk of seriously damaging work relations, social relations, family relations, or personal dignity." As already detailed in the introduction, the current study adopted the CAARMS definition of the BLIPS. Accordingly, seriously disorganizing and dangerous features have been conceptualized as nonpsychotic predictors of longitudinal outcomes.

Study Measures

Cross-sectional Analysis (Diagnostic Significance of BLIPS). The primary measure was baseline ICD-10 diagnosis of nonorganic psychosis in UHR individuals meeting BLIPS (ie, schizophrenia spectrum psychoses, ATPD, affective psychoses, substance use psychoses, delusional disorders, unspecified nonorganic psychoses, post puerperium psychosis).

Longitudinal Analysis (Prognostic Significance of BLIPS). Primary outcome measure for the longitudinal analysis was risk of psychosis over time. Predictors of psychosis onset included sociodemographic factors (age, gender, borough, ethnicity, marital status, employment status) and clinical factors (Health Of the Nation Outcome Scale, HoNOS[14] total score, baseline Social and Occupational Functioning Assessment Scale (SOFAS),[15] CAARMS P1–P4[2] total score, BLIPS duration, BLIPS subgroup, BLIPS recurrence, presence of seriously disorganizing or dangerous features). BLIPS recurrence was defined as the onset of a second episode of psychosis lasting less than 7 days and not meeting psychosis threshold on the CAARMS 12/2006.[2] Psychosis onset was operationalized according to the CAARMS 12/2006.[2]

Procedure

ICD-10 diagnoses of psychosis and other study measures (with the exception of seriously disorganizing or dangerous features, see below) were automatically extracted by 1 researcher with the use of the Clinical Record Interactive Search (CRIS) tool[16] (see supplementary eMethods for details on CRIS).

Seriously disorganizing and dangerous features were selected through medical records screening by 2 independent psychiatrists who were blind to the outcome of BLIPS, under the supervision of a clinician who underwent the SIPS/SOPS training.

Statistical Analysis

Sociodemographic and clinical characteristics of the sample were described with mean and SD for continuous variables and absolute and relative frequencies for categorical variables. The primary outcome of the cross sectional analysis (diagnostic significance of BLIPS as compared with ICD-10) was investigated with absolute and relative frequencies tables. The primary outcome of the longitudinal analysis (prognostic significance of BLIPS) was investigated with Kaplan–Meier failure function (1-survival)[17] and Greenwood 95% CIs,[18] indicating the risk of transition to psychosis during the follow-up. The impact of sociodemographic and clinical factors predicting psychosis onset was investigated using Cox proportional hazards models evaluating the effects of potential predictors on psychosis onset and time to transition, after checking for proportional hazards assumption.[19] Predictor factors have been detailed above here. As previously described,[20] in the first stage of factors selection, all potential factors were computed individually in univariate Cox regression analysis. Factors that remained significant at a liberal statistical threshold ($P < .25$)[21] were entered into a multivariate model, built using backward (stepwise, likelihood ratio method) inclusion ($P < .05$). The −2 log-likelihood ratio test was used to evaluate the overall significance of the predictive Cox regression model. The Wald chi-square statistic was used to test the significance of individual factors in the model. This model was generated using the Akaike information criterion modified for survival analyses.[22] Bootstrap resampling ($\beta = 10\,000$ bootstrap samples) was used to test the robustness of the final predictive model.[23] Apparent model calibration was assessed by plotting the Cox predicted curves and comparing them with the Kaplan–Meier observed survival curves for the same variable. We further computed Receiver Operating Characteristics (ROC) curve to test the apparent discriminative ability of the selected model to predict psychosis onset. We used the risk of developing psychotic disorders as reference standard and the selected predictor as index test. We estimated the summary sensitivity and specificity, positive and negative likelihood ratios. We also estimated the Area Under the Curve (AUC).[24] The AUC serves as a global measure of test performance. Values in the range of 0.9–1 are considered outstanding, between 0.8 and 0.9 are considered excellent, between 0.7 and 0.8 are considered acceptable.[25]

For all the analyses above here, statistical tests were 2-sided and statistical significance was defined as P values of less than .05. All analyses were conducted in SPSS, version 22.0 (SPSS, Inc) or STATA 13 (STATA Corp).

Results

Sociodemographic and Clinical Characteristics of the Sample

As shown in table 1, 80 individuals with BLIPS (59% males) attended the OASIS service until December 2015. Their mean age was 25 years, 72% were single and 40% unemployed. Proportion of white (48%) and black (45%) ethnicities was similar. Most individuals with BLIPS (61%) did

Table 1. Clinical and Sociodemographic Characteristics of UHR individuals With BLIPS Detected by the OASIS Service (n = 80)

	N	Mean	SD
Age (y)	80	25.06	5.45
Baseline SOFAS	70	57.93	14.14
HoNOS (adjusted total)	45	9.91	7.26
CAARMS P1–P4 total score[a]	80	50.93	17.49
BLIPS duration (days)	80	6.17	1.13
	N	Count	%
Gender	80		
Females		33	41.30
Males		47	58.80
Borough	77		
Lambeth		41	53.25
Southwark		26	33.78
Other		10	12.97
Ethnicity	80		
White		38	47.50
Black		36	45.00
Other		6	7.50
Marital status	76		
Married		4	5.26
Separated or divorced		3	3.95
Single		55	72.37
In a relationship		14	18.42
Employment status	77		
Employed		25	32.47
Student		21	27.27
Unemployed		31	40.26
BLIPS subgroup	80		
BLIPS only		49	61.30
BLIPS+APS		26	32.50
BLIPS+GRD		1	1.30
BLIPS+APS+GRD		4	5.00
BLIPS seriously disorganizing or dangerous	75		
No		55	73.33
Yes		20	26.67
BLIPS recurrence	76		
Single episode		68	89.47
Recurrent episodes		8	10.53

Note: BLIPS, Brief Limited Intermittent Psychotic Symptoms; OASIS, Outreach and Support in South London; CAARMS, Comprehensive Assessment of At Risk Mental State; APS, Attenuated Psychosis Symptoms; HoNOS, Health Of the Nation Outcome Scale; GRD, Genetic Risk and Deterioration Syndrome; SOFAS, Social and Occupational Functioning Assessment Scale.
[a]Computed as P1 severity × P1 frequency + P2 severity × P2 frequency + P3 severity × P3 frequency + P4 severity × P4 frequency.
[b]5 individuals had 2 episodes and 3 individuals had 3 episodes, time to BLIPS recurrence, mean 267 days, 95% CI 0–592, median 121 days, range 32–1203.

not meet other UHR subgroups criteria. About one-third (27%) had seriously disorganizing or dangerous features according to SIPS/SOPS. BLIPS lasted on average 6 days.

Diagnostic Significance of BLIPS

About two-thirds of BLIPS (68%, table 2) received a baseline ICD-10 diagnosis of ATPD. The vast majority of ATPD cases were characterized by schizophrenic symptoms: acute polymorphic psychotic disorder with symptoms of schizophrenia and acute schizophrenia-like psychotic disorder (44/54 = 78%). Conversely, acute polymorphic psychotic disorder without symptoms of schizophrenia accounted for 7% (4/54) of ATPD cases only. The second most frequent ICD-10 baseline psychotic diagnosis in individuals with BLIPS was unspecified nonorganic psychosis (15%), followed by mental and behavioral disorders due to use of cannabinoids (11%) and mania with psychotic symptoms (6%).

Table 2. Baseline ICD-10 Diagnoses in UHR Individuals Meeting BLIPS criteria at the OASIS Service (n = 80)

	ICD-10 Code[26]	*N*	%
Acute and transient psychotic disorder	F23	54	68
Acute polymorphic psychotic disorder without symptoms of schizophrenia	*F23.0*	*4*	*5*
Acute polymorphic psychotic disorder with symptoms of schizophrenia	*F23.1*	*22*	*28*
Acute schizophrenia-like psychotic disorder	*F23.2*	*20*	*25*
Other acute and transient psychotic disorders	*F23.8*	*7*	*9*
Acute and transient psychotic disorder, unspecified	*F23.9*	*1*	*1*
Unspecified nonorganic psychosis	F29	12	15
Mental and behavioral disorders due to use of cannabinoids	F12	9	11
Acute intoxication	*F12.0*	*8*	*10*
Dependence syndrome	*F12.2*	*1*	*1*
Manic episode	F30	5	6
Mania with psychotic symptoms	*F30.2*	*5*	*6*

Note: BLIPS, Brief Limited Intermittent Psychotic Symptoms; OASIS, Outreach and Support in South London. Diagnostic subtypes in italics fall under the umbrella of the main diagnostic categories.

Prognostic Significance of BLIPS

The mean follow-up time was of 881 days (SD = 1038.44). Over follow-up, 8 individuals (11%) had recurrent episodes of BLIPS, 5 individuals had 2 episodes and the remaining 3 experienced 3 episodes over a median period of 121 days.

Risk of Psychosis in BLIPS. There were 28 conversions to psychosis (failures) over the follow-up time. The failure function (figure 1) was: at 3 months 0.102 (95% CI 0.053–0.194), at 6 months 0.144 (95% CI 0.082–0.244), at 12 months 0.189 (95% CI 0.117–0.301), at 24 months 0.303 (95% CI 0.205–0.435), at 36 months 0.467 (95% CI 0.335–0.621), at 48 months 0.497 (95% CI 0.360–0.652), at 60 months 0.543 (95% CI 0.394–0.701). The mean time to event was 2363 days (ie, 6.47 y), SD 287, 95% CI 1802-2925 (median 1788 d, ie, 4.89 y).

Univariate Cox Regression Analysis. The univariate cox regression analysis revealed that seriously disorganizing

or dangerous features (hazard ratio [HR] = 3.637, 95% CI 1.680–7.874) and BLIPS recurrence (6 out of 8 recurrent BLIPS developed psychosis, HR 3.989, 95% CI 1.589–10.011) increased significantly the risk of psychosis. The remaining factors being studied such as age, HoNOS, SOFAS, CAARMS P1–P4 total score, BLIPS duration, gender, borough, ethnicity, marital status, employment status, and BLIPS subgroup were not significant (table 3).

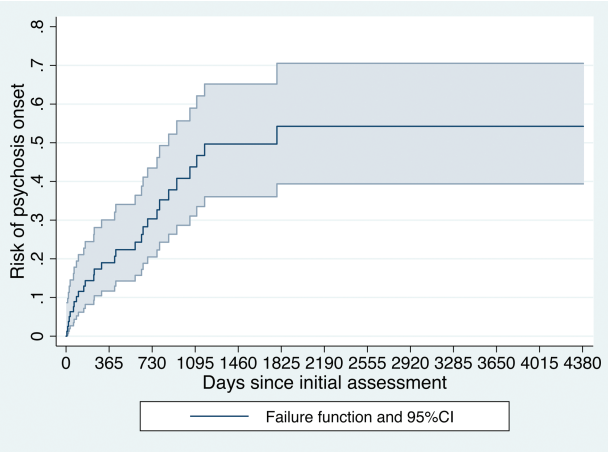

Fig. 1. Kaplan–Meier failure function (risk of psychosis onset) with 95% CIs in Brief Limited Intermittent Psychotic Symptoms (BLIPS) individuals (n = 80). The last transition to psychosis was observed at 1788 d since initial assessment at the Outreach and Support in South London (OASIS).

Multivariate Cox Regression Analysis. The final predictive model included seriously disorganizing or dangerous features only (HR = 4.391, 95% CI 1.370–14.078, table 3). The failure function, stratified for absence or presence of seriously disorganizing or dangerous BLIPS features (figure 2) was respectively: at 3 months 0.056 (95% CI 0.019–0.165) and 0.250 (95% CI 0.112–0.501), at 6 months 0.076 (95% CI 0.029–0.191) and 0.350 (95% CI 0.185–0.597), at 12 months 0.124 (95% CI 0.057–0.257) and 0.401 (95% CI 0.229–0.656), at 24 months 0.209 (95% CI 0.112–0.368) and 0.631 (95% CI 0.404–0.853), at 36 months 0.312 (95% CI 0.174–0.521) and 0.778 (95% CI 0.547–0.943), at 48 months 0.369 (95% CI 0.212–0.590) and 0.778 (95% CI 0.547–0.943), at 60 months 0.369 (95% CI 0.212–0.590) and 0.889 (95% CI 0.639–0.991). Visual inspection of apparent model calibration plot (supplementary efigure 1) shows good agreement between predicted and observed risk.

Model Robustness. Bootstrapping confirmed that the multivariate cox regression equation based on seriously disorganizing or dangerous features was not overfit to the

Table 3. Clinical and Sociodemographic Factors Predicting the Onset of Psychosis in UHR individuals meeting BLIPS criteria (n = 80) (Cox Regression Analyses)

	Log-Likelihood χ^2	Sig	β	SE	Hazard Ratio	95% CI		Wald	*P*
Univariate analysis									
Age (y)	0.984	0.321	0.034	0.035	1.035	0.967	1.108	0.977	.323
HoNOS	2.721	0.099	0.049	0.030	1.051	0.990	1.115	2.653	.103
SOFAS	0.242	0.623	0.008	0.016	1.008	0.977	1.039	0.242	.623
CAARMS P1–P4 total score	1.030	0.310	0.012	0.012	1.012	0.989	1.036	1.028	.311
BLIPS duration (d)	1.803	0.179	0.053	0.039	1.054	0.976	1.139	1.781	.182
Gender[a]	0.317	0.574	−0.217	0.386	0.805	0.377	1.716	0.316	.574
Borough[b]	1.056	0.590	0.115	0.474	1.122	0.443	2.843	0.059	.808
Ethnicity[c]	0.326	0.850	0.170	0.393	1.185	0.549	2.559	0.186	.666
Marital status[d]	0.830	0.842	0.323	0.621	1.381	0.409	4.665	0.270	.603
Employment status[e]	0.199	0.905	−0.182	0.458	0.833	0.340	2.044	0.158	.691
BLIPS subgroup[f]	0.699	0.873	0.186	0.393	1.205	0.558	2.601	0.226	.635
BLIPS seriously disorganizing or dangerous[g]	12.305	<0.001	1.291	0.394	3.637	1.680	7.874	10.740	.001
BLIPS recurrence[h]	10.116	0.001	1.383	0.470	3.989	1.589	10.011	8.681	.003
Multivariate analysis[i]									
BLIPS seriously disorganizing or dangerous[g]	7.368	0.007	1.480	0.594	4.391	1.370	14.078	6.196	.013

Note: BLIPS, Brief Limited Intermittent Psychotic Symptoms; CAARMS, Comprehensive Assessment of At Risk Mental State; HoNOS, Health Of the Nation Outcome Scale; APS, Attenuated Psychosis Symptoms; SOFAS, Social and Occupational Functioning Assessment Scale.
[a]Females vs males.
[b]Southwark vs Lambeth.
[c]Black vs white.
[d]Single vs in a relationship.
[e]Employed vs unemployed.
[f]BLIPS+APS vs BLIPS only.
[g]Seriously disorganizing and dangerous vs not seriously disorganizing and dangerous.
[h]Recurrent vs not recurrent.
[i]Factors selected from univariate analysis: HoNOS, BLIPS duration, BLIPS seriously disorganizing or dangerous, BLIPS recurrence.

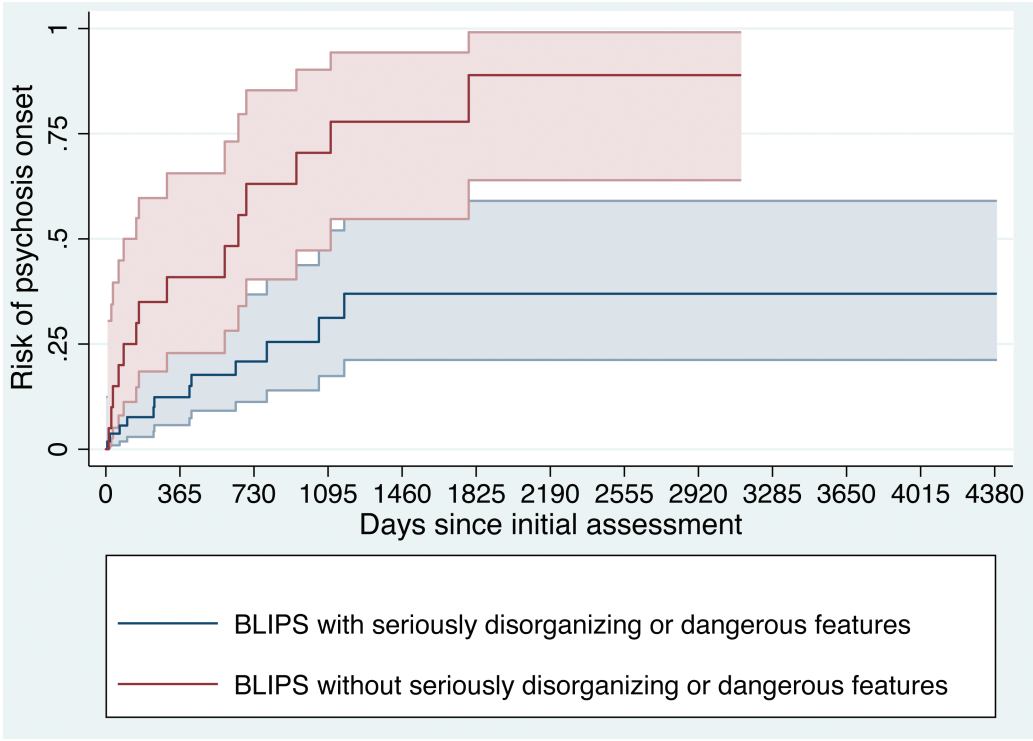

Fig. 2. Kaplan–Meier failure function (risk of psychosis onset) and 95% CIs in Brief Limited Intermittent Psychotic Symptoms (BLIPS) individuals ($n = 80$) stratified for the presence of seriously disorganizing or dangerous features. Log-rank $\chi^2 = 12.31$, $P = .001$.

data: HR 3.637, SE 1.44, $Z = 3.18$, $P < .001$, 95% CI 1.64–8.07, Wald 10.09, $P = .002$.

ROC Analysis. The ROC analysis indicated an apparent sensitivity of 0.70, apparent specificity of 0.78 for the presence of seriously disorganizing or dangerous features. The presence/absence of these features correctly classified 0.76 of cases developing psychosis with a likelihood positive ratio of 3.21 and a likelihood negative ratio of 0.38. The apparent AUC was of 0.74 (95% CI from 0.62 to 0.86).

Discussion

To our knowledge this is the first original study of CAARMS-defined BLIPS ever conducted. Since it is based on a large sample and long-term follow-up, it makes clear advances from earlier observations in several ways. First, it enhances the understanding of the diagnostic significance of BLIPS by investigating their relationship with competing ICD-10 diagnoses. We found that most BLIPS met ICD-10 criteria for ATPD (68%) followed by unspecified nonorganic psychosis (15%), mental and behavioral disorders due to use of cannabinoids (11%) and mania with psychotic symptoms (6%). Second, it examines a number of clinical and sociodemographic factors and makes it possible to point out specific predictors for BLIPS, while at the same time highlighting some conceptual limitations. We found that about 1 in 2 BLIPS individuals developed a psychotic disorder over time (5-year failure 0.54). Recurrent BLIPS episodes were relatively infrequent (11%) but associated with higher risk of psychosis onset at the univariate analysis (HR = 3.98). The best predictor of psychosis onset at the multivariate analysis was the presence of seriously disorganizing or dangerous features, which was associated with an extreme high risk (HR = 4.39, 5-year failure 0.89) of transitioning to psychosis.

The first aim of the current study was to address the diagnostic significance of the BLIPS compared to competing ICD-10 diagnoses. Our study's findings suggest that about two-third of BLIPS cases met the diagnostic criteria for ATPDs, further corroborating our recent meta-analytical findings of comparable risk of psychosis between BLIPS and ATPD constructs.[7] Conceptually, the BLIPS definition has more coherence with the ATPD construct as compared to other first-episode diagnoses. Because of this conceptual overlay, depending on the local availability of high-risk services, young adults presenting with brief psychotic episodes may equally receive a diagnosis of established psychosis and start an antipsychotic treatment (as ATPD/BPD), or an at-risk diagnosis (as BLIPS/BIPS) and undergo psychological interventions.[27] To overcome these inconsistencies these categories should be further compared, rather than abandoned, as suggested by other publications in this special issue.[28,29] Comparative analyses may specifically benefit the UHR research, because there is more knowledge into the epidemiology, course and outcomes of ATPD (eg, large follow-up studies with up to 5426 individuals[30]) than in the

BLIPS construct (only the current study available). For example, it may be argued that the BLIPS is diagnostically pluripotent and that it is not specific for schizophrenia spectrum psychoses. However, the meta-analytical risk of developing affective psychoses is actually higher in ATPD than in BLIPS (eFigure 4 from Fusar-Poli et al[9]). Thus, there is more evidence for pluripotential outcomes in ATPD than in BLIPS,[31] with up to one-third of initial ATPD cases transitioning to affective psychoses.[32] In fact, we found that BLIPS tend to overlap (78% of baseline BLIPS meeting ATPD criteria) with the ATPD subtypes characterized by schizophrenic symptoms: acute polymorphic psychotic disorder with symptoms of schizophrenia (F23.1) and acute schizophrenia-like psychotic disorder (F23.2). This is probably because BLIPS encompass Schneider's first-rank symptoms, which have been incorporated into the ICD-10 criteria for schizophrenia. Conversely, ATPD constitutes a heterogeneous category including subtypes with polymorphic, schizophrenic and prevalently delusional symptoms, which are likely to herald longer lasting psychotic and affective disorders.[28] While acute polymorphic psychotic disorder lasts less than 3 months and refers to the earlier concepts of "bouffée délirante and cycloid psychosis," featuring varied delusions, hallucinations, perceptual changes, perplexity, and emotional turmoil shifting daily or even faster, the ATPD subtypes with schizophrenic symptoms are set apart from schizophrenia only by temporal criteria of less than 1 month. The available evidence suggests that these subtypes have a high risk to evolve into schizophrenia over the short and longer terms.[30] The overlap between BLIPS and ATPD schizophrenic subtypes is also consistent with meta-analytical evidence indicating the UHR state specifically predicts schizophrenia spectrum psychoses (73% of transitions) rather than affective psychotic outcomes (11% of transitions only).[33] Recent original studies in UHR individuals (n = 271) as contrasted to comparison individuals (n = 171) further confirmed no evidence of diagnostic pluripotentiality with respect to new or incident anxiety, bipolar, or non-bipolar mood disorders.[34]

The second aim of the current study was to address the prognostic significance of the BLIPS under the CAARMS framework and to address the impact of sociodemographic and clinical predictors of psychosis onset. The overall risk of psychosis in the long term (5-year) was 0.54 and it is in line with recent meta-analytical estimates in brief psychotic episodes.[7] This value is also very similar to the 0.56 meta-analytical proportion of diagnostic instability observed from an initial ATPD.[35] The univariate analysis revealed that recurrent BLIPS, although not frequent, had a 4-fold increase in this risk (HR = 3.89) compared to mono-episodic BLIPS. Recurrent BLIPS may have a significant prognostic relevance because repeated episodes of BLIPS would not qualify as transition to psychosis under the CAARMS 12/2006 but rather still as UHR state. However, we found that the vast majority (6/8) of individuals presenting with recurrent BLIPS eventually developed a psychotic disorder (lasting more than 7 d). As the 2 individuals who did not develop psychosis had used cannabis during their index episode, it is possible to speculate that recurrent BLIPS not associated with drug abuse may almost inevitably transit to psychosis. This result, if validated by future studies, would question the clinical utility of a 7-day observation window and watchful and waiting strategies for recurrent BLIPS, advocating more assertive monitoring and focused treatments.

However, BLIPS recurrence did not survive the multivariate analysis, which selected only the presence of seriously disorganizing or dangerous BLIPS features as core predictive factor for BLIPS outcomes, with a 4-fold increase in risk (HR = 4.39). It is possible to hypothesize that the SIPS/SOPS authors had introduced this exclusion criterion on the assumption that this BLIPS subgroup would present with symptoms and behavior that were too extreme to qualify for a state of risk. Such an assumption remained untested for about 2 decades, until our bootstrapping analysis confirmed the robustness of their poor prognostic significance in the CAARMS framework. The BLIPS without seriously disorganizing or dangerous features showed a 5-year 0.37 risk of developing psychosis, as compared with the 5-year 0.89 for the seriously disorganizing or dangerous BLIPS. This was also reflected by an acceptable apparent test performance as observed with the AUC. The high-transition risk in seriously disorganizing or dangerous BLIPS may truly reflect the presence of extreme state factors that are close to the psychosis threshold,[36] as hypothesized by the SIPS/SOPS authors (see clinical implications below). They may have elaborated the seriously disorganizing or dangerous exclusion criterion on the basis of their earlier work on psychopathological subtypes of schizophrenia indicating that a drift toward disorganization (hebephrenia, see supplementary eDiscussion for details) was associated with "deterioration" and poorer functional outcome.[37]

Implications for Clinical Practice and Research

There may be some implications for clinical practice and research. The current findings contribute to the recent accumulating evidence pointing to the BLIPS distinctiveness as compared to the other UHR subgroups.[31,38] Our results indicate that BLIPS represent natural fluctuations of psychosis in individuals with psychotic disorder.[4] Furthermore, it has been argued that the 7-day duration proposed for the BLIPS would be a "clinically meaningful point" (page 134)[39] to initiate antipsychotic treatments for UHR individuals, in order to minimize overtreatment of false positives. However, no studies show that a 7-day cutoff is effective in doing so. In clinical practice, the introduction of BLIPS has not completely prevented antipsychotic treatments of UHR individuals. The findings of our recent meta-analysis revealed that about 30% of BLIPS (or BIPS)

individuals did receive antipsychotic treatments as routine clinical practice of high risk services in the past 2 decades.[6] More to point, the BLIPS construct is not strictly necessary to promote a delayed introduction of antipsychotic medication in favor of potentially safer interventions. In fact, comprehensive psychosocial interventions are already under development for patients receiving a standard diagnosis of first-episode psychosis.[40] Furthermore, the 7-day cutoff and current UHR treatments are based on the assumption that the UHR group is homogeneous. Conversely, our meta-analysis indicated that there is a differential level of risk of developing psychosis across different UHR subgroups (BLIPS>APS>GRD).[6] This suggests that there may be different clinically meaningful points for initiating treatments across BLIPS, APS, GRD subgroups or even within the same subgroup. Stratified interventions targeting the differential level of risk for psychosis in UHR subgroups should be specifically considered by updated international guidelines. Another publication in the current special issue is presenting a pilot attempt to integrate these findings into a developmental clinical staging model that is based on hierarchical symptom severity.[29] In this model, BLIPS cases represent the most severe clinical stage preceding the psychosis onset.

Another implication relates to the clinical significance of disorganizing or dangerous features. Whether these features are predictors of psychosis onset from an at-risk state or early markers of recurrent psychotic disorders already present at baseline clearly depends on the variable psychosis threshold[4] adopted by the CAARMS vs the SIPS. Indeed, disorganizing or dangerous features generate substantial diagnostic disagreement across the 2 instruments (for a full discussion see our previous comparative CAARMS vs SIPS analysis[10]). It is well known that the point at which an individual crosses the line from high risk or UHR state to psychosis threshold is arbitrary.[41] However, the historical association of disorganized symptoms with poor outcomes, reviewed in the supplementary eDiscussion, and the fact that these features yielded an extreme risk of psychosis in CAARMS-defined BLIPS individuals who were already meeting criteria for ATPD may suggest that these individuals have already passed the psychosis threshold at baseline. Unfortunately this finding is of limited psychometric utility in the field, because disorganizing or dangerous features are not operationalized in the available UHR instruments and therefore likely to be affected by assessment biases (see other limitations in the supplementary eLimitations).

Conclusions

BLIPS were most likely to meet the criteria for ICD-10 diagnosis of ATPD at intake, mainly the subtypes with schizophrenic symptoms. About half of BLIPS cases developed a psychotic disorder over follow-up. Recurrent BLIPS were relatively infrequent but tended to transit to psychosis. Seriously disorganizing or dangerous features were associated with an extreme risk of psychosis.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

Funding

This study was supported in part by a 2014 NARSAD Young Investigator Award to P.F-P.

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*. 2013;70:107–120.
2. Yung A, Yuen H, McGorry P, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *ANZJP*. 2005;39:964–971.
3. Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. *Schizophr Bull*. 1996;22:283–303.
4. Fusar-Poli P, Van Os J. Lost in transition: setting psychosis trehsold in prodromal research. *Acta Psychiatr Scand*. 2013;127:248–252.
5. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull*. 2003;29:703–715.
6. Fusar-Poli P, Cappucciati M, Borgwardt S, et al. Heterogeneity of risk for psychosis within subjects at clinical high risk: meta-analytical stratification *JAMA Psychiatry*. 2016;73:113–120.
7. Fusar-Poli P, Cappucciati M, Bonoldi I, et al. Prognosis of brief psychotic episodes: a meta-analysis. *JAMA Psychiatry*. 2016;73:211–220.
8. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull*. 2003;29:703–715.
9. Fusar-Poli P, Cappucciati M, Bonoldi I, et al. Prognosis of brief psychotic episodes: a meta-analysis. *JAMA Psychiatry*. 2016;73:211–220.
10. Fusar-Poli P, Cappucciati M, Rutigliano G, et al. Towards a standard psychometric diagnostic interview for subjects at ultra high risk of psychosis: CAARMS versus SIPS. *Psychiatry J*. 2016;2016:7146341.
11. Fusar-Poli P, Byrne M, Badger S, Valmaggia LR, McGuire PK. Outreach and support in south London (OASIS), 2001–2011: ten years of early diagnosis and treatment for young individuals at high clinical risk for psychosis. *Eur Psychiatry*. 2013;28:315–326.

12. Fusar-Poli P, Frascarelli M, Valmaggia L, et al. Antidepressant, antipsychotic and psychological interventions in subjects at high clinical risk for psychosis: OASIS 6-year naturalistic study. *Psychol Med*. 2015;45:1327–1339.
13. McGlashan TH, Walsh B, Wood SJ. *The Psychosis-Risk Syndrome. Handbook for Diagnosis and Follow-up*. New York, NY: Oxford University Press; 2010.
14. Orrell M, Yard P, Handysides J, Schapira R. Validity and reliability of the Health of the Nation Outcome Scales in psychiatric patients in the community. *Brit J Psychiatry*. 1999;174:409–412.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed., text rev. Washington, DC: American Psychiatric Association; 2000.
16. Stewart R, Soremekun M, Perera G, et al. The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. *BMC Psychiatry*. 2009;9:51.
17. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Amer Statist Assn*. 1958;53:457–481.
18. Greenwood M. *The Natural Duration of Cancer*. London, UK: HMSO; 1926.
19. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515–526.
20. Cornblatt B, Carrión R, Auther A, et al. Psychosis prevention: a modified clinical high risk perspective from the Recognition and Prevention (RAP) Program [published online ahead of print June 5, 2015]. *Am J Psychiatry*.
21. Hosmer D, Lemeshow S. *Applied Logistic Regression*. 2nd ed. New York, NY: Wiley; 2000.
22. Akaike H. Likelihood of a model and information criteria. *J Econom*. 1981;16:3–14.
23. Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. *Stat Med*. 1992;11:2093–2109.
24. Obuchowski NA, Lieber ML, Wians FH Jr. ROC curves in clinical chemistry: uses, misuses, and possible solutions. *Clin Chem*. 2004;50:1118–1125.
25. Hosmer W, Lemeshow S. *Applied Survival Analysis: Regression Modeling of Time to Event Data*. New York, NY: Wiley & Sons; 1999.
26. World Health Organization. *International Classification of Diseases, Tenth Revision (ICD-10)*. Geneva, Switzerland: WHO; 1990.
27. Fusar-Poli P, Yung AR, McGorry P, van Os J. Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention. *Psychol Med*. 2014;44:17–24.
28. Queirazza F, Semple DM, Lawrie SM. Transition to schizophrenia in acute and transient psychotic disorders. *Brit J Psychiatry*. 2014;204:299–305.
29. Carrion R, Correll C, Auther A, Cornblatt B. A severity-based clinical staging model for the psychosis prodrome: longitudinal findings from New York RAP study. *Schizophr Bull*. 2017;43:64–74.
30. Castagnini A, Foldager L. Epidemiology, course and outcome of acute polymorphic psychotic disorder: implications for ICD-11. *Psychopathology*. 2014;47:202–206.
31. Fusar-Poli P, Rutigliano G, Stahl D, et al. Long-term validity of the at risk mental state (ARMS) for predicting non-psychotic mental disorders. *Eur Psychiatry*. In press.
32. Castagnini AC, Munk-Jorgensen P, Bertelsen A. Short-term course and outcome of acute and transient psychotic disorders: differences from other types of psychosis with acute onset. *Int J Soc Psychiatry*. 2016;62:51–56.
33. Fusar-Poli P, Bechdolf A, Taylor MJ, et al. At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. *Schizophr Bull*. 2013;39:923–932.
34. Webb JR, Addington J, Perkins DO, et al. Specificity of incident diagnostic outcomes in patients at clinical high risk for psychosis. *Schizophr Bull*. 2015;41:1066–1075.
35. Fusar-Poli P, Cappucciati M, Rutigliano G, et al. Diagnostic stability of ICD/DSM first episode psychosis diagnoses: meta-analysis. *Schizophr Bull*. 2017;43:48–56.
36. Cornblatt BA, Carrion RE. Deconstructing the psychosis risk syndrome: moving the field of prevention forward. *JAMA Psychiatry*. 2016;73:105–106.
37. McGlashan TH, Fenton WS. Subtype progression and pathophysiologic deterioration in early schizophrenia. *Schizophr Bull*. 1993;19:71–84.
38. Addington J, Liu L, Perkins D, Carrion RE, Keefe R, Woods SW. The role of cognition and social functioning as predictors in the transition to psychosis for youth with attenuated psychotic symptoms. *Schizophr Bull*. 2017;43:57–63.
39. Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophr Res*. 2004;67:131–142.
40. Francey SM, Nelson B, Thompson A, et al. Who needs antipsychotic medication in the earliest stages of psychosis? A reconsideration of benefits, risks, neurobiology and ethics in the era of early intervention. *Schizophr Res*. 2010;119:1–10.
41. Yung AR, Nelson B, Thompson A, Wood SJ. The psychosis threshold in Ultra High Risk (prodromal) research: is it valid? *Schizophr Res*. 2010;120:1–6.